In Harm's Way: Infections in Deployed American Military Forces

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Hundreds of thousands of American service members have been deployed to Afghanistan and Iraq since 2001. With emphasis on the common infections and the chronic infections that may present or persist on their return to the United States, we review the data on deployment-associated infections. These infections include gastroenteritis; respiratory infection; war wound infection with antibiotic-resistant, gram-negative bacteria; Q fever; brucellosis; and parasitic infections, such as malaria and leishmaniasis.

The disruption of societies, the crowded conditions, and the associated stresses brought on by war have resulted in epidemics of infection that involve both combatants and local civilian populations. Infections following the receipt of battle wounds have historically been commonplace [1, 2]. The development of better sanitation and hygiene practices and the improved prevention and treatment of infections through the use of vaccines and antibiotics have considerably decreased the incidence and impact of wartime infections [1]. Despite this, infectious diseases remain an important concern in the current conflicts in Iraq and Afghanistan.

Although combat-related injuries are often the most severe and dramatic health risks encountered during wartime, disease and nonbattle injuries are more common [3, 4]. Disease and nonbattle injuries include noncombat orthopedic injuries, mental health/combat stress, and gastrointestinal, respiratory, and dermatologic conditions. In reviewing data from aeromedical evacuations from Iraq in 2003, disease and nonbattle injuries were found to be 6 times more common than battle injuries [5]. Although infectious diseases were only specified in 2.8% of the diagnoses, many cases classified as diseases of the digestive tract, respiratory system, and skin and that involved ill-defined symptoms were likely infections [5]. Furthermore, three-quarters of personnel have experienced diarrhea, and more than two-thirds have had respiratory infections, with an increased incidence during combat operations (figure 1) [6]. There have been reports of leishmaniasis [7, 8], malaria [9], pneumonia [10], Q fever [11], brucellosis [12], and wounds infected with multidrug-resistant *Acinetobacter* species [13].

Because ~36% of the military personnel currently deployed in Iraq and Afghanistan are from Reserve and National Guard units, it is very possible that some of these soldiers will present to civilian physicians on return to the United States [14]. This review summarizes the various infections that are being observed in soldiers returning from Iraq and Afghanistan.

GASTROENTERITIS

In the initial phases of operations in both Afghanistan and Iraq, large outbreaks of severe gastroenteritis secondary to norovirus and *Shigella* infections were reported in both British and American personnel [15–17]. Subsequently large outbreaks were less frequently reported, but diarrhea remained a common problem. More personnel deployed to Iraq than to Afghanistan experienced at least 1 episode of diarrhea (77% vs. 54%; $P < .0001$). Personnel in Iraq also tended to experience symptoms of greater severity and a longer duration of illness and were more likely to have multiple episodes [6]. Rates of diarrhea correlated with local food consumption [18]. Most episodes lasted <1 week, but 10% of cases lasted >14 days. Among cases that lasted ⩾14 days, there was no association with functional bowel symptoms, but there was an association with weight loss and blood in the stool [18].

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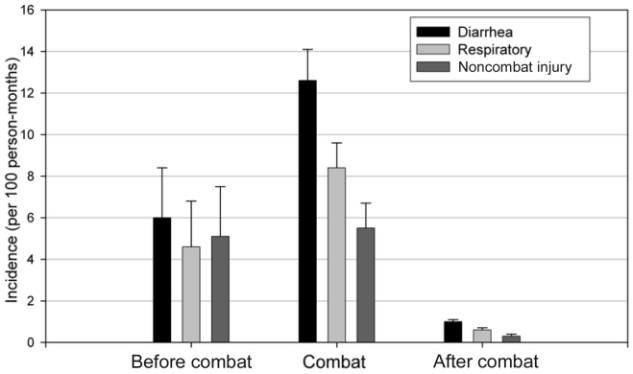

Figure 1. Incidence of illness and noncombat injury among US Military personnel during initial combat operations in Iraq, 2003. *Bars,* 95% CIs.

In the summer of 2004, a surveillance study in Iraq found that 66% of troops had diarrhea, and 50% experienced multiple episodes. Field laboratory testing found that enterotoxigenic *Escherichia coli* (23%) and enteroaggregative *E. coli* (12.5%) were the most common pathogens, whereas norovirus (2.5%) and *Shigella* species (0.8%) were much less common [19]. Although it was not associated with acute diarrhea, ~1% of volunteers were found to have *Entamoeba histolytica,* and an additional 7% had various other protozoan commensals. In the summer of 2005, an evaluation of an outbreak of diarrhea among US military personnel in Iraq found *Cryptosporidium* species present in >50% of subjects (Dennis Faix, US Navy Forward Deployed Preventive Medicine Unit-East, personal communication). Thus, soldiers who present with chronic diarrhea should be evaluated for postinfection irritable bowel syndrome and for parasites such as *Giardia* species, *Cryptosporidium* species, and *E. histolytica* [20].

RESPIRATORY ILLNESS

Self-reported survey information was collected from >15,000 homeward-bound members of the American military during 2004, and respiratory illness was commonly reported (69% of persons experienced 1 episode, and 14% experienced >3 episodes) [6]. Pneumonia was described by 3% of persons, most of whom received treatment in an ambulatory setting. Nearly 40% reported that they smoked more than half a pack of cigarettes per day, with 48% being first-time smokers or former smokers who restarted during deployment. Data from this survey did not show a link between respiratory illness and smoking cigarettes made by non-US manufacturers [6].

During the period from March 2003 through March 2004, several cases of severe pneumonia were reported. The clinical presentation included rapid onset of cough, dyspnea (with or without fever), and leukocytosis. Bilateral alveolar infiltrates and often a need for mechanical ventilation were noted. Some of these patients had definite or probable acute eosinophilic pneumonia. This rare idiopathic disease is characterized by pulmonary infiltrates noted on a chest radiograph, eosinophilic infiltration of the lung, and respiratory failure. In the year mentioned above, there were 18 cases of acute eosinophilic pneumonia identified among 183,000 military personnel deployed in or near Iraq; 2 cases were fatal [10]. Despite an extensive epidemiologic investigation, no common exposure source or infectious etiology was identified, and new-onset smoking was the only reported association. Three patients had elevated titers consistent with *Coxiella burnetti* seroconversion [11]. There have been at least 8 persons with acute eosinophilic pneumonia among US soldiers (regardless of deployment) since March 2004, one of whom had onset of symptoms 1 month after returning from Iraq [21]. Early case identification is essential, because prompt therapy with corticosteroids has been associated with a favorable outcome.

TUBERCULOSIS (TB)

TB is endemic in central and southwest Asia, with the World Health Organization (WHO) estimating an incidence of smear-positive TB of 143 cases per 100,000 persons in Afghanistan and of 58 cases per 100,000 person-years in Iraq in 2003 [22]. Regional conflicts pose significant challenges for surveillance of this communicable disease. The American military uses PPD (purified protein derivative of tuberculin) screening before and after deployment. The overall deployment-associated conversion rate is ~2.5% [23]. The number of cases of active TB among service members that have been attributed to infection acquired in Iraq or Afghanistan has been negligible to date.

Q FEVER

Q fever is a zoonotic infection due to *C. burnetii* that is usually acquired through inhalation of infected particle aerosols. This typically results from direct contact with the reservoir hosts (commonly cattle, goats, and sheep), but it may occur after exposure to contaminated manure, straw, or dust kicked up by vehicles. Other routes of transmission include tick bites and ingestion of raw milk [24]. Infection presents acutely as either a self-limited febrile ("flu-like") illness, pneumonia, or hepatitis [24]. It can also present as a chronic infection, most commonly as endocarditis [25].

In Iraq, Q fever was identified in US military personnel during an evaluation of an apparent outbreak of severe pneumonia. Eight patients with pneumonia were found to have antibodies against *Coxiella* species [11]. Of the initial 3 patients, all reported extensive animal exposure, 2 had a history of tick bites, and 1 drank raw goat's milk [11]. In addition, 2 patients with febrile hepatitis received a diagnosis of Q fever (Todd Gleeson, National Naval Medical Center, personal communication), and 22 cases were identified during an investigation of a febrile respiratory illness among 38 Marines in western Iraq

[26]. Early recognition of these cases and a search for underlying valvulopathies is important, so that appropriate treatment can be instituted to prevent endocarditis [27].

WAR WOUND INFECTION

Nearly 18,000 members of the US military have been wounded in action while serving in Iraq or Afghanistan [28]. Because of the nature of injuries (wounds caused by improvised explosive devices, mortars, rocket-propelled grenades, and gunshots) and protective gear, extremity wounds are prevalent. The bacteriology of these wounds has been a significant factor in determining antibiotic prophylaxis and treatment guidelines. Bacteria that contaminate wounds during the initial trauma are different from those cultured from infected wounds later in time. The bacteriology of war wound infections in posttrauma patients has shifted from *Clostridia* species in World War I, to *Streptococcus pyogenes* and *Staphylococcus aureus* in World War II, to gram-negative bacilli (*Pseudomonas aeruginosa, Enterobacter* species, *E. coli,* and *Klebsiella* species) since the Vietnam War [29–32]. This shift is attributed to early wound debridement (thereby reducing the impact of *Clostridia* infection), as well as to treatment with antibiotics (thereby reducing the incidence of infection due to gram-positive pathogens).

During Operation Iraqi Freedom, samples from war wounds were obtained shortly after injury for aerobic culture [33]. Approximately one-half of the culture results were positive, with most cultures yielding gram-positive skin flora. In Iraq, the wounded are rapidly evacuated to skilled surgical teams and are treated with early debridement of wounds. Prophylactic antibiotics are selected on the basis of the anatomic site of injury. Similar to previous wars, wound infections develop days after injury and are largely due to gram-negative organisms, including *P. aeruginosa, Klebsiella* species, and *E. coli,* which are usually acquired in the hospital setting. Bacteria found in current wound infections are commonly multidrug resistant and include the *Acinetobacter calcoaceticus–Acinetobacter baumannii* complex *(Acinetobacter).*

Acinetobacter *infection.* The outbreak of *Acinetobacter* infection among military personnel has created management challenges due to multidrug resistance, nosocomial transmission, and difficulties in differentiating infection from colonization. *Acinetobacter* is a ubiquitous, opportunistic pathogen and is reportedly the most common gram-negative bacteria to colonize the skin of hospital personnel [34]. Early laboratory Gram stain findings (i.e., from Gram stains before organism identification) can be misleading because of the pleomorphic appearance of the bacterium [35]. Preliminary investigations using genetic characterization indicate that nosocomial transmission of *Acinetobacter* species occurs throughout the military health care system (Paul Scott, Army Medical Surveillance Activity, personal communication). Similar infectious complications occur in hospitalized victims of natural disasters; suboptimal debridement of devitalized tissue and environmental contamination may play a role in acquisition of *Acinetobacter* species and infection [36, 37].

Since 2003, the incidence of multidrug-resistant *Acinetobacter* infection in military treatment facilities has increased significantly. The majority of isolates are cultured from wound specimens; however, the increase in incidence has involved all culturable sites, including blood. At Walter Reed Army Medical Center (Washington, DC), there were 0.087 cases of *Acinetobacter* bloodstream infection per 1000 admissions in 2002; in 2005, there were 0.3 cases per 1000 admissions. The majority of *Acinetobacter* isolates cultured from hospitalized, injured personnel have been multidrug resistant, unlike isolates cultured before the war (figure 2). Whole-genome sequencing of a resistant, epidemic strain showed that *A. baumannii* was able to switch genomic structures, likely accounting for the rapid resistance mutation acquisition under antibiotic pressure [38].

The decision of when and for how long to treat a patient with positive culture results—particularly wound cultures—has been as challenging as deciding which antibiotics should be used. The wounds resulting from war injuries frequently involve traumatic amputation, large soft-tissue defects, and skeletal trauma with exposed bone [4]. Once all devitalized tissue has been resected, if the wound appears to be infected or if there are systemic signs of infection without an alternate source, treatment is guided by susceptibility results for the wound culture pathogen. Treatment of *Acinetobacter* wound infections (18 with osteomyelitis, 2 burns, and 3 deep wounds) at a tertiary care military hospital resulted in successful outcomes with no relapses of all patients [39]. We recommend combination antibiotic therapy for the treatment of *Acinetobacter* infection when the patient is critically ill, immunocompromised, or has significant comorbidities. Because of multidrug resistance, we repeatedly rely on the polymyxins for treatment, according to in vitro susceptibility testing using the Kirby-Bauer disk diffusion method [40]. Despite the challenge of treating patients with multidrug-resistant *Acinetobacter* infection, related mortality in the previously healthy host remains low.

Nosocomial transmission has resulted in fatalities that are directly attributable to *Acinetobacter* infection in immunocompromised civilian patients. Intensified infection-control measures have been implemented during transit to the United States. Upon arrival to US military treatment facilities, hospitalized, injured personnel are placed in contact isolation and tested for *Acinetobacter* skin colonization. If axilla and groin skin swab culture results are negative, then the patient is removed from isolation. From November 2004 through January 2006, there was a 15% incidence of *Acinetobacter* skin colonization among injured personnel (Charlotte Carneiro, Walter

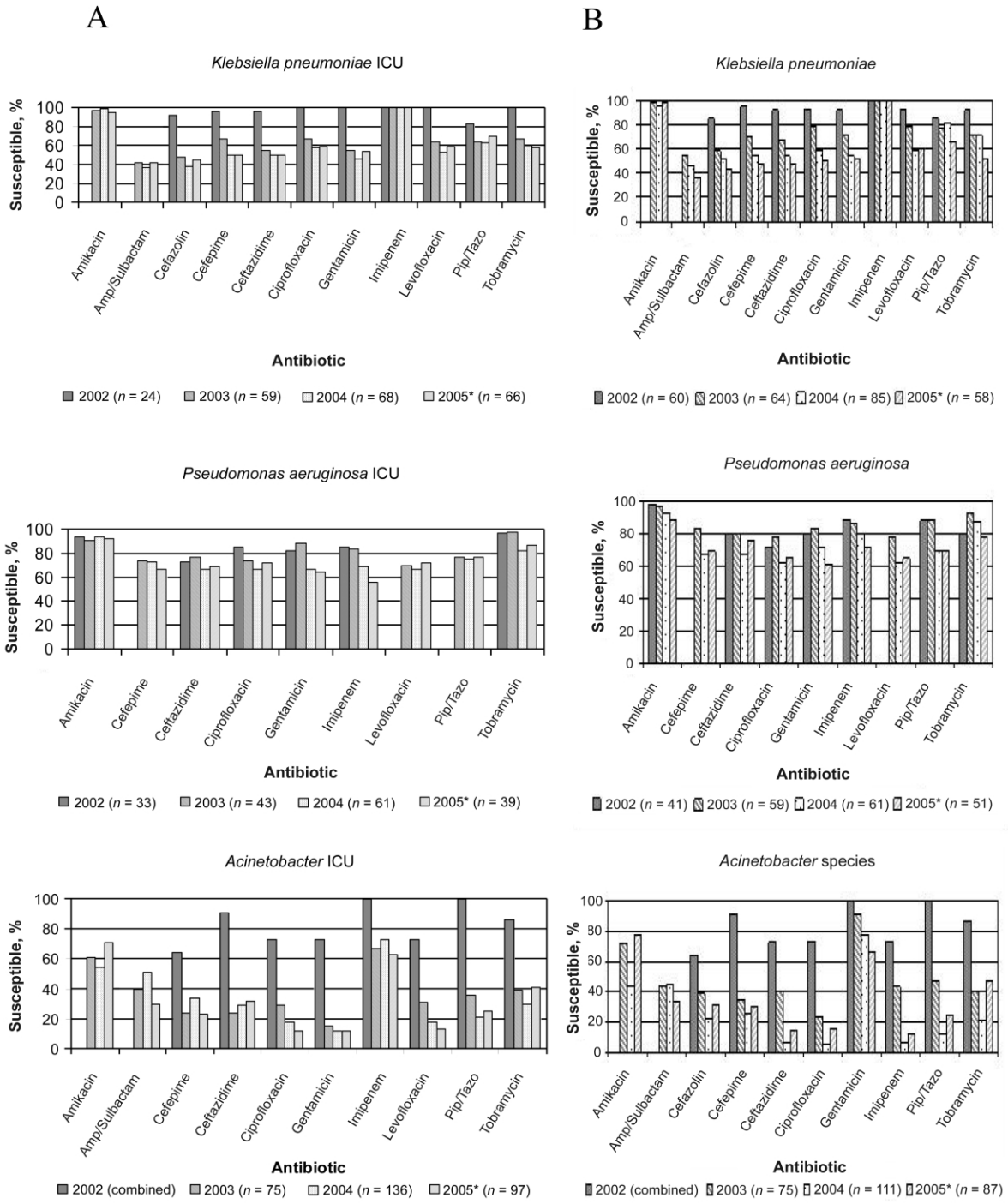

Figure 2. Changes in antibiotic susceptibility among intensive care unit (ICU) isolates *(A)* and inpatient isolates *(B)* of *Klebsiella pneumoniae, Pseudomonas aeruginosa,* and *Acinetobacter* species from 2002–2005. Amp, ampicillin; Pip/Tazo, piperacillin-tazobactam. *1 January through 31 October 2005

Reed Army Medical Center Infection Control Service, personal communication).

Other microorganisms associated with war wounds. Although *Acinetobacter* infections have been newsworthy, *E. coli*, *Klebsiella pneumoniae* (commonly extended spectrum β-lactamase–producing *K. pneumoniae*), and *P. aeruginosa,* like *Acinetobacter* species, are being isolated with increasing frequency and with increasing antibiotic resistance (figure 2). Unlike *Acinetobacter* infection, infection caused by these organisms, even if it occurs in previously healthy hosts, appears to result in significant morbidity and mortality.

Emphasis on infection-control mechanisms—particularly

hand washing—is required to limit the nosocomial spread of multidrug-resistant bacteria. Prudent use of antibiotics, the selection of which is based on evidence of infection and susceptibility patterns, is needed to control the evolution of increasing resistance of multidrug-resistant pathogens in the hospital setting.

MALARIA

Malaria remains of significant military operational importance in areas of endemicity. In 2004, *Plasmodium vivax* infection acquired in Afghanistan accounted for 25% of the 56 malaria cases diagnosed among US Army soldiers; soldiers presented for care weeks to 20 months after return to the United States [41]. In contrast, there have been no reported cases of malaria acquired in Iraq among US military forces. In Iraq, chloroquine-susceptible *P. vivax* infection occurs at low rates (150 cases per year in 2004) [42]. This contrasts with the 261,456 malaria cases in Afghanistan, as reported to the WHO in 2004; 80% of these cases involve *P. vivax,* but *P. falciparum* is also transmitted [42]. A report of a soldier who acquired *P. vivax* malaria in Afghanistan detailed a clinically severe infection with acute respiratory distress syndrome and relapse, despite the administration of primaquine (30 mg per day for 14 days). Primaquine tolerance was postulated [43]. An outbreak of *P. vivax* infection among Army Rangers was reported after deployment to eastern Afghanistan. The observed malaria attack rate was 52.4 cases per 1000 soldiers, with the diagnosis made 1–339 days (median, 233 days) after return to the United States [9]. In this unit, the self-reported rates of adherence to mefloquine prophylaxis and terminal primaquine prophylaxis were 52% and 31%, respectively [9].

LEISHMANIASIS

From March 2003 until June 2005, an estimated 0.23% of deployed US ground forces in Operation Iraqi Freedom received a diagnosis of leishmaniasis (Paul Scott, personal communication). This protozoan infection is usually transmitted by the bite of an infected sand fly. Most reported cases of cutaneous infection have originated from exposure in Iraq; *Leishmania major* is overwhelmingly the most common species. In contrast, during the Afghanistan deployment, the transmission of *L. major, Leishmania tropica,* and *Leishmania infantum-donovani* have been identified. Although *L. major* infection is restricted to the skin, with occasional lymphocutaneous extension, the other species of *Leishmania* may be associated with visceralization and more chronic, reactivating illness.

The clinical presentation of cutaneous leishmaniasis in American soldiers is generally chronic, painless skin lesion(s), which are often ulcerative and have a dry, scaling eschar; however, the appearance can vary [44]. Diagnosis depends on parasitologic confirmation through skin sampling with scraping, slit skin smear, or biopsy. Both culture and PCR permit speciation of *Leishmania* species, and this may have implications for management. Treatment for the usually self-limited *L. major* infection (which can persist for 6–12 months) includes watchful waiting, cryo- or heat therapy, and administration of azoles, topical paromomycin, and the pentavalent antimonials (intralesional and parenteral); systemic therapies are used for larger lesions, multiple lesions, and cosmetically problematic lesions. In contrast, infection with *L. tropica* and *L. infantum* are often treated more aggressively with systemic therapies. Treatment may not eradicate the persistent intracellular organism, but it does control clinical disease [45]. Because of this, there are future implications with regard to reactivation of *L. infantum* or *L. tropica* infection in hosts who subsequently become immunocompromised. Military policy dictates lifelong deferral of blood donation for persons who receive a diagnosis of any type of leishmaniasis, regardless of whether they have received treatment [46].

Visceral leishmaniasis is a form of leishmaniasis that can be asymptomatic, subclinical, or symptomatic and that manifests with chronic fever, pancytopenia, hepatosplenomegaly, and cachexia. In Iraq, visceral leishmaniasis has been mostly reported from the more southern regions, especially among malnourished children [47]. Of the 5 cases of visceral leishmaniasis that occurred among US military personnel, all parasites that were speciated were *L. infantum-donovani,* and the incubation period varied, but it could be prolonged as much as 14 months after returning from the combat theater [8, 48]. Results of serologic assays—specifically, the rk39 immunochromatographic assay (Inbios International) and the *Leishmania* immunofluorescence assay (Centers for Disease Control and Prevention)—proved to be positive for all of our cases of visceral leishmaniasis. Specific parasitologic diagnosis should be sought; this requires obtaining tissue biopsy specimens (such as bone marrow, liver, lymph node, or spleen biopsy specimens) for histopathologic examination, parasite culture, and PCR. Treatment with liposomal amphotericin B has been effective.

BRUCELLOSIS

Brucellosis is a zoonotic disease endemic to the Middle East and transmitted to humans through contact with infected animals. *Brucella* bacteria may be ingested, inhaled, or percutaneously inoculated. There were 3 reports of brucellosis during the period of 2003–2005. One of these cases occurred in a US Army helicopter pilot after a 5-month deployment in Iraq (blood culture grew *Brucella melitensis*); he had observed the slaughter of a sheep, but he denied ingestion of unapproved animal or dairy products [12].

OTHER

Studies assessing the rates of arboviral infection, including Sand Fly Fever virus, Sindbis virus, West Nile virus, and Rift Valley Fever virus are underway. To date, seroconversion has been uncommon (<3%), with no association with a history of febrile illness (Kenneth Earhart, US Navy Medical Research Unit–3, personal communication).

There have been several cases of ophthalmomyiasis among coalition forces in Iraq. This disease presents with the abrupt onset of conjunctivitis. The motile, mucoid, flat-segmented larvae (size, <1 mm) can be seen attached to bulbar and palpebral conjunctiva. Ophthalmomyiasis is caused by *Oestrus ovis,* the sheep nasal botfly, which often strikes the eye or can deposit the larvae in the eye through a close fly-by. Occasionally, this infestation can involve the globe (ophthalmomyiasis interna) and can result in sight-threatening complications [49].

Typhoid fever is a public health concern in Iraq and Afghanistan, with risk primarily related to a lack of safe water and food. Multidrug-resistant (including ciprofloxacin-resistant) *Salmonella enterica* serotype Typhi has been identified in Iraq [47]. American forces are vaccinated before deployment, and no cases have been reported to date. Parasitic infections, such as schistosomiasis and echinococcus, have not been reported among US forces.

CONCLUSIONS

Combat injuries are the most dramatic health risk of war, but nonbattle injuries, such as infectious diseases, have led to more lost duty time and hospitalization in every US major war for centuries [50]. Appropriate public health and preventive measures have minimized the incidence of many illnesses for our soldiers, but further prevention of vector- and foodborne infections may provide additional protection. We highlighted the types of infections that our military has acquired related to deployments in Iraq and Afghanistan, sharing practical issues of epidemiology, diagnosis, and management that follow from our experience.

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ERRATUM

In an article in the 15 October 2006 issue of the journal (Aronson NE, Sanders JW, Moran KA. In harm's way: infections in deployed American military forces. Clin Infect Dis 2006; 43: 1045–51), an error appeared in figure 2*B*. Under "*Acinetobacter* species," the x-axis should read "Amikacin, Amp/Sulbactam, Cefepime, Ceftazidime, Ciprofloxacin, Gentamicin, Imipenem, Levofloxacin, Pip/Tazo, Tobramycin" (*not* "Amikacin, Amp/Sulbactam, Cefazolin, Cefepime, Ceftazidime, Ciprofloxacin, Gentamicin, Imipenem, Pip/Tazo, Tobramycin"). The corrected figure panel appears below. The journal regrets this error.

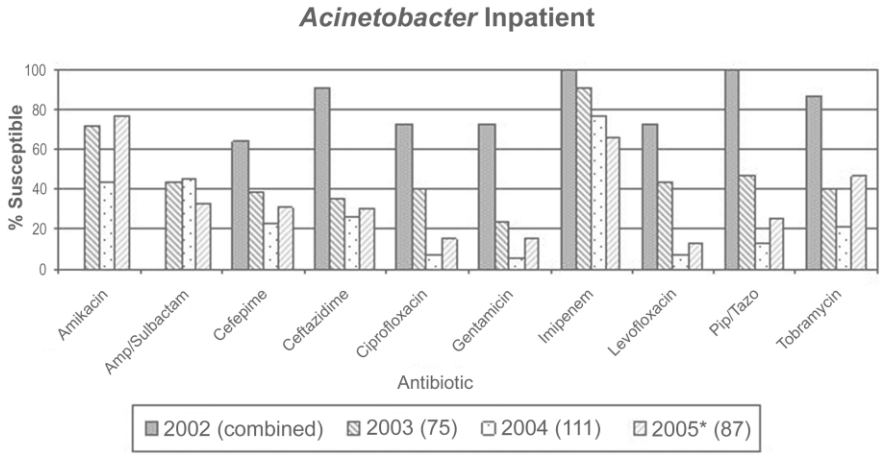

Figure 2*B*. Amp, ampicillin; Pip/Tazo, piperacillin-tazobactam

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